REMARKS

Claims 1-3, 7, and 9-14 are currently pending in the present application.

1. Amendments to the Claims

Claim 1 has been amended to clarify the claim. Support for the amendments is found in the Specification at page 1, lines 10-14, page 2, lines 20-22, page 6, lines 15-16, page 17, line 25, page 20, line 26-28, and page 23, lines 19-24.

Claims 8 and 15 are herein cancelled.

No new matter has been added.

2. Rejection under 35 U.S.C. § 112, First Paragraph

a. Claim 15

The Examiner rejects claim 15 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants herein cancel claim 15, thereby obviating the rejection. Applicants request that it be withdrawn.

b. Substrate

The Examiner rejects presumably only claim 15 as lacking sufficient written description for the recitation of "substrate used in the method which comprises a first surface part and an opposite second surface part . . .." Applicants note that the Examiner has not indicated which claims are rejected, as is required by 37 C.F.R. § 1.104(c) "if the invention is not considered patentable . . . the claims, or those considered unpatentable will be considered." (See MPEP § 706.) Solely in order to further prosecution, Applicants present arguments in response to the Examiner's rejection. However, Applicants submit that because specific claims were not rejected, this rejection is inadequate.

The Examiner states that the substrate used in the method comprising a first surface and a second surface is not supported by the Specification using words, structures and formulas. However, Applicants submit that the Examiner's rejection fails because the words in combination with the drawings of the Specification would indicate to one of skill in the art at the time of filing would have understood that Applicants had possession of such a structure.

The words supporting the description of the substrate include the disclosures on pages 17, lines 1-4, page 13, lines 4-26, and page 19, lines 4-8 of the Specification. Drawings supporting description of the substrate and Figures 2 and 3.

As a matter of law, drawings can provide sufficient written description. The MPEP states that:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, **figures**, **diagrams**, and formulas that fully set forth the claimed invention.

MPEP § 2163 (I), citing *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1621, 1966 (Fed. Cir. 1997) (emphasis added). The Examiner's arguments do not acknowledge that the case law explicitly advocates that written description support can be found in the drawings. Therefore, Applicants submit that their reliance on the drawings is proper.

Furthermore, the content of the drawings supports Applicants' claim language. Figure 3 shows a profile view of a substrate of the claimed invention. The black "rectangle" labeled 1, is broadly characterized as the "chip housing." On the left hand side of the chip housing there are two openings 6, the "inlet port/pipetting well for introduction of cells and compound" leading to channel 4, the "cell containing channel/compartment containing extracellular buffer solution and compound, and the opening leading to 5, the channel containing intracellular buffer solution and mRNA from cell in whole-cell configuration." (See page 3, description of Figure 3.)

These channels form two paths through the substrate, between which is item 3 a glass or silica membrane on microstructured unit. (Page 13, line17 and figure 3.) This membrane is has one or more "cell capture site[s]" or "test sites." (Page 13, line 23, and page 16, line 28 referring to figure 3, and page 17, lines 1-3.)

As shown in Figure 2 these test sites have a small opening to allow for genotypic detection of heterologous DNA, but also allow electrophysiology analysis. (Page 13, lines 4-10.) The test site is where a "whole cell has been brought into contact with the substrate at a measuring site and has been punctured, or by means of a pore-forming substance, has been opened to electrical contact with the cell interior." (Page 18, lines 26-29.) Thus, as discussed with reference to figure 3, the upper channel (extracellular buffer) is in contact with surface one

of the membrane having a plurality of test sites. The second surface is the surface of the membrane in contact with the intracellular buffer.

Accordingly, Applicants submit that the combination of the drawings and the words in the Specification are sufficient to establish that Applicants had possession of the claimed method at the time of filing. Applicants request that the rejection be withdrawn.

3. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-2 and 7-13 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (*see Office Action, page 5-7*). Applicants respectfully traverse.

a. Heterologous DNA Sequence

The Examiner maintains that "heterologous DNA sequence" is unclear. Applicants respectfully disagree. Heterologous is a term well-known in the art of cell biology and genetics. As the specification describes, DNA, which is not from the cell itself, *i.e.*, which is heterologous to the DNA of the cell, is introduced into a cell. (Specification, page 8, line 26-28.) DNA is introduced into a host cell to be expressed. (Specification, page 1, line 5.) Multiple types of DNAs to be introduced are described, such as the various types of DNA libraries. (Specification, page 6, line 15 to page 8, line 24.)

None of these DNAs would naturally occur in the cell otherwise; *i.e.*, these DNAs are not part of the host cell's normal DNA contents. Applicants attach a basic Google search for the term "heterologous DNA" for the Examiner's convenience, which evidences the common usage of the term.

Structurally, the introduced DNA itself is not need not be bound to another type of molecule, *i.e.*, a reporter. In the biological arts, the term "heterologous DNA" is used to indicate DNA which is introduced into a cell, which need not have any other special structural features. Accordingly, Applicants submit that the term is clear and request that the rejection be withdrawn.

b. Cell of Interest

Applicants submit that the "cell of interest" as described on page 2, lines 13-14 of the Specification is designated "of interest" based on the physiological properties conferred to said cell by the heterologous DNA which is expressed in said cell. The Specification describes a non-limiting example of this:

> An example of the influence of the expressed recombinant protein [i.e., the expressed heterologous DNA] influencing cellular conditions occurs when the expressed recombinant protein is a cell membrane ion channel. Both the intracellular and extracellular conditions are affected. An ion channel allows and/or causes the movement ions across cellular membranes. . . . and therefore changes the ion concentration both intra- and extra- cellularly.

Specification, page 5, lines 10-16. Thus, in the example, introducing a heterologous DNA into a host cell which encodes a cell membrane ion channel, and expressing said heterologous DNA in the host leads to a measurable phenotypic change in the ion concentrations intra- and extracellularly. Cells become "of interest", when they exhibit such a phenotypic change.

With regard to the "cell and/or genetic material of interest is derived from the heterologous DNA", Applicants submit that the phenotypic change indicating that a cell is of interest is derived from the heterologous DNA and that genetic material of interest (*i.e.*, the heterologous DNA and/or mRNA), identified by the method of the invention may then be characterized or recovered from said cell of interest. See Specification, page 22, lines 4-21, describing multiple methods to isolate genetic material, but preferably mRNA, from said cell of interest, including pipetting, lysis, and a mechanical scraping. From that genetic material, mRNA, including the mRNA transcript of the heterologous DNA, can be isolated and characterized. The method of mRNA isolation is standard in the art. Accordingly, Applicants submit that said "cell of interest" is clear to one of skill in the art and request that the Examiner withdraw the rejection.

c. Genetic Material

As discussed above with regard to the "cell of interest", the "genetic material" in claim 1 and in Figure 2 includes all of the genetic material from the cell. As discussed above, the genetic material from the cell includes the heterologous DNA and/or mRNA. As described in the claim, mRNA is ultimately isolated from the cell of interest. Applicants submit that one of skill would understand exactly what is claimed. Applicants request that the rejection be withdrawn.

d. Part of a cDNA Library

Applicants submit that the concept of making and practice of using cDNA libraries is customary in the art. A cDNA library is "a collection of cloned cDNA (complementary DNA) fragments inserted into a collection of host cells, which together constitute some portion of the

"transcriptisome" of an organism. The transcriptisome is a set of all messenger RNA molecules produced in a cell. Therefore, the library is produced from mRNA, so it only contains genes that are expressed in the source organism or tissue. Molecules of a vector, each containing different cDNA fragments, will be produced and used to transfect the plurality of host cells. Thus, each host cell may potentially express a different cDNA fragment, which, in the context of the present invention, may confer a different electrophysiological property on said host cell.

The vector and its own genes are not technically part of the cDNA library, as the purpose of the library is a stock of multiple vectors carrying the individual cDNA fragments to be examined. Thus, the vector is a convenient storage for cDNA fragments that may be transfected into multiple host cells to screen for desirable properties, conferred on the cells by the stored cDNA fragments.

This is basic knowledge in the art.

Thus, each individual heterologous cDNA sequence may be considered to be part of the cDNA library, as described in Specification, at page 2, lines 20-22.

Accordingly, Applicants submit that the claims are clear and request the Examiner withdraw the present rejection.

e. Spaced-Apart

The Examiner rejects claim 13 stating that "spaced-apart" locations are indefinite as to how or what the spacing of the cells is such that each is apart from each other. Applicants submit that the Examiner's rejection is unreasonable in view of the disclosure in the Specification and the knowledge in the art.

The Examiner appears to have failed to understand the basic aspects of the invention. As discussed above, the invention provides a substrate with a plurality of test sites or measuring sites. The purpose of these test sites is to perform both electrophysiological analysis and genetic analysis. To perform electrophysiological analysis, the test sites are "adapted to provide a high electrical resistance seal" between the cell and the surface part of the site. (Specification, page 17, lines 13-15). Said high electrical resistance seal is characterized as a "giga seal" at the site. *Id.* Thus, one cell is in contact with one set of electrodes at a time, and as shown in figure 2, one cell is in a test site at a time. Thus, one of skill would recognize that the "spaced-apart" means

that the test site is designed such that only one cell may be present at a time, and that multiple cells will not be in contact with each other.

Accordingly, Applicants request that the Examiner withdraw the rejection.

f. First Surface Part and Opposite Surface Part

As discussed above, the combination of the drawings and the words in the Specification are supported and Applicants submit, these disclosures render the claim language clear to one of skill in the art.

With regard to the plurality of sites adapted to hold an ion channel and whether the ion-channel containing structure is the heterologous DNA, Applicants submit the following comments. The ion channel containing structure of the invention is a cell or cell membrane. (Specification, page 17, line 25 and page 18, line 29 to page 19, line 2.)

The sites of the first part of the construct can be thought of as similar to the patch clamp pipettes, but are planar surfaces with a patch clamp orifice as described in WO 02/029402 (now issued as U.S. 6,932,893).

The cell being tested is positioned on the orifice, usually by virtue of pressure differences between the lower liquid reservoir and the cell containing medium. The cell therefore adheres to the test site.

Accordingly, Applicants submit that the claimed method is clear based on the disclosure in the Specification. Applicants request that the rejection be withdrawn.

g. Claims 8 and 15

Applicants submit that claims 8 and 15 have been cancelled. Applicants request that the rejection be withdrawn.

4. <u>Rejection under 35 U.S.C. § 102(e)/103(a)</u>

a. Qin

The Examiner rejects claims 1-2, 7-13, and 15 under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Qin *et al.* (US 6,994,993).

Applicants respectfully traverse. Qin does not anticipate or make obvious the presently claimed invention because it does not meet each element of the claims.

Substrate

Qin does not disclose the substrate of the present invention. The currently claimed method requires "a substrate for making the electrophysiological measurements upon which at least one cell can be arranged on the substrate comprising a first surface part and an opposite second surface part, wherein the first part has a plurality of sites each of which is adapted to hold a cell or cell membrane." Qin does not disclose a substrate with two surfaces, one of which has sites for holding the cell.

Heterologous DNA and cDNA Libraries

The currently claimed method requires "providing a plurality of cells which collectively comprise a cDNA library, each cell comprising a heterologous DNA sequence." Qin describes transfecting cells with a known nucleic acid encoding a protein human β1A. Qin does not transfect a plurality of cells with a library so as to identify nucleic acids encoding proteins affecting cell electrophysiology. Rather, Qin measures the effect of small molecules on a single known ion channel, for example Qin is looking for a "modulater of human β1A, which has the potential to disrupt specific ion channel activity or cell surface expression of human β1A." Qin, column 20, lines 50-54.

Isolating and removing mRNA

The present invention requires isolating the cell of interest, and/or genetic material from the cell of interest; and isolating mRNA which is transcribed from the heterologous DNA from the cell of interest. The disclosure of Qin does not address isolating mRNA which is transcribed from the heterologous DNA. Based on Qin, there would be no purpose, as the DNA introduced into the cells of Qin is known. (See Qin, column 20, lines 32-35.) Moreover, there is no extraction of the mRNA from the cell being investigated, or isolation (by PCR) of the mRNA transcribed from the heterologous DNA.

Accordingly, Applicants submit that Qin does not disclose or make obvious the instantly claimed method. Applicants request that the rejection be withdrawn.

b. Maher

The Examiner rejects claims 1-2, 7-13, and 15 under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Maher *et al.* (US 6,969,449).

Like, Qin discussed above, Maher does not disclose every element of the claimed invention. Like Qin, the DNA introduced into the cell is known at the time of the electrophysiological measurement. In contrast, the DNA of the present method is unknown at the time of electrophysiological measurement and is subsequently characterized.

Applicants therefore request that the rejection be withdrawn.

CONCLUSION

In view of the above amendments, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Gerald M. Murphy Reg. No. 28,977, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

Dated: March 19, 2009

Respectfully submitted,

By _____

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Attached: Google Search dated February 16, 2009